M E M O R A N D U M

Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research

To: File (STN 125392/0 BLA EVARREST™ SBRA Addendum)

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For: Original Biological License Application (BLA) STN 125392/0- Omrix's EVARREST, Fibrin Sealant Patch, Non-clinical Labeling for Revised Summary Basis for Regulatory Action (SBRA)

Synopsis

This addendum contains the final, recommended nonclinical language for inclusion in the revised summary basis for regulatory action (SBRA) for EVARREST™ Fibrin sealant patch, based on review of the pharmacology and toxicology information submitted in the application STN BLA 125392/0. The SBRA has been revised to be consistent with further discussions related to the final EVARREST review. The final modified language for the SBRA is listed below:

4. Nonclinical Pharmacology/Toxicology

Pharmacological/Toxicological Findings

EVARREST was determined to be safe for its intended use as an adjunctive hemostat, based on data from nonclinical studies (Good Laboratory Practices [GLP] and non-GLP compliant), and its clinical use in surgical settings both within and outside of the United States. The nonclinical program consisted of a series of studies to demonstrate the safety and effectiveness of EVARREST. Completed nonclinical studies included safety pharmacology (rats), efficacy (rats, minipigs, and beagles), local tolerance (rabbits, minipigs, and dogs), antigenicity (guinea pigs, rats, and minipigs), mutagenicity, degradation, immunogenicity (guinea pigs), and acute toxicity studies (minipigs and dogs). EVARREST was evaluated in controlled nonclinical studies, according to its intended clinical use (i.e. as an adjunct to hemostasis). These studies compared the safety and effectiveness of the EVARREST fibrin pad with the results obtained using other adjunctive hemostatic methods (manual compressions, or another cleared or approved

hemostatic product) as controls. Adverse findings were reported in both the control and EVARREST arms, including thromboembolic events, re-bleeding at treatment bleeding site, persistent inflammation, hemorrhage at wound site, and adhesion formation at treatment bleeding site. These adverse findings could be expected based on EVARREST's mechanism of action, were predictive of adverse reactions later reported in the clinical trials, and were similar in incidence to previous experience with analogous products following administration (i.e., post-operative re-bleeding, neutralizing antibody formation, and thromboembolic events). Long-term animal studies to evaluate the carcinogenic potential of EVARREST or studies to determine its genotoxicity or effects on fertility have not been performed. Ethicon has completed an assessment of the carcinogenic risk of the EVARREST fibrin pad to address potential long-term adverse effects from product use. The information submitted to the BLA suggests that the carcinogenic potential of this product should be minimal, and comparable to similar products currently marketed in the United States.

b) Pharmacokinetics

EVARREST was acutely tested in animals at up to 10 times the intended clinical dose (approximately 1 standard size pad/surgery; 10 pads tested) in a single procedure, for up to two weeks without any adverse events reported. Pharmacokinetic studies demonstrate that degradation of the fibrin sealant component of EVARREST begins within hours, as the fibrin is metabolized by fibrinolysis and phagocytosis. However, small remnants of EVARREST may be present up to 8 weeks after application (approximately 5% of patch remaining in animal studies), with remnants degrading exponentially.

Conclusion:

The non-clinical safety profile determined for EVARREST is sufficient to support the safe use of EVARREST in the proposed indication as an adjunct to hemostasis. Therefore, the Pharmacology/Toxicology Reviewer recommends approval of this BLA.